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Improving treatment and imaging in ADPKD

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Estimation of total kidney volume in ADPKD

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ABSTRACT

Background: Measuring total kidney volume (mTKV) in autosomal dominant polycystic kidney disease (ADPKD) by magnetic resonance image (MRI) and manual tracing is time consuming. Two alternative MRI methods have recently been proposed to estimate TKV ($eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$) which require less time.

Methods: ADPKD patients with a wide range of kidney function and an approved T2 weighted MRI performed at the University Medical Centers of Groningen, Leiden, Nijmegen and Rotterdam, the Netherlands from 2007 to 2014. Test-set for assessing reproducibility n=10, cohort for cross-sectional analyses n=220, and cohort for longitudinal analyses n=48. Performances of the gold standard method of manual tracing kidney volumes were compared to both estimation methods.

Results: In the test-set, intra- and inter-coefficients of variation for mTKV, $eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$ were 1.8 and 2.3%, 3.9 and 6.3%, and 3.0 and 3.4%, respectively. In cross-sectional analysis, baseline mTKV, $eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$ were 1.96 (1.28-2.82), 1.93 (1.25-2.82) and 1.81 (1.17-2.62) liters, respectively. In cross-sectional analysis, Bias was 0.02±3.2, 1.4±9.2 and 4.6±7.6% for repeat mTKV, $eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$, respectively. In longitudinal analysis, no significant differences were observed between % change in measured TKV (16.7±17.1%) and % change in $eTKV_{ELLIPSOID}$ (19.3±16.1%) and $eTKV_{PANK}$ (17.8±16.1%) over three years.

Conclusions: Both methods for eTKV perform relatively well compared to mTKV, and can detect change in TKV over time. Since $eTKV_{ELLIPSOID}$ requires less time than $eTKV_{PANK}$, we suggest this method may be preferable in clinical care.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the formation and growth of numerous cysts in both kidneys, leading to an increase in kidney volume. These cysts compress healthy kidney tissue, causing progressive kidney function decline, and in most patients ultimately a need for renal replacement therapy. In ADPKD patients, total kidney volume (TKV) has shown to be an early marker of disease severity and predictor of kidney function decline[1]. Measurement of TKV is therefore used to assess prognosis in clinical care and for selection of patients for randomized controlled trials[2]. In these trials that investigate potential treatments for ADPKD patients assessment of TKV is often used as primary or secondary study endpoint[3-5].

The true gold standard method to assess TKV is the manual tracing method. Computer Tomogram or Magnetic Resonance Images (MRI) is used, in which per slice the kidney boundaries are traced manually using dedicated software. mTKV is calculated from a set of contiguous images by summing the products of the area measurements within the kidney boundaries and slice thickness[6]. This method is laborious, which limits its use in trial settings, but especially in clinical care.

In case kidney volume could be estimated with sufficient accuracy and reliability, it would alleviate the time consuming process of kidney volume measurement. Recently, two kidney volume estimation methods have been developed: the mid-slice method by the CRISP consortium[7] and the ellipsoid method by the Mayo Clinic[2]. For both methods, measured and estimated kidney volumes appeared to be well correlated, but other groups have yet not validated these methods. In addition, the mid-slice method was developed in a cohort that included only patients with a creatinine clearance >70 ml/min. Such patients have in general relatively small kidneys making manual tracing measurement of TKV relatively easy, which may have influenced the results that were obtained. This method should therefore also be validated in patients with lower kidney function. Estimation methods to assess TKV may also be used in clinical trials, but only when they can accurately and reliably detect changes in TKV over time. To our knowledge these issues have not been investigated yet.

Given these considerations, the objective of the present study was to investigate cross-sectionally the aforementioned methods to estimate TKV in a patient group with a wide range of kidney function. Furthermore, we investigated in a longitudinal study whether these estimation methods can accurately detect changes in TKV.

Chapter 9

METHODS AND MATERIALS

Patients and study design

For this study, all MRIs of ADPKD patients that were available from 2007 to 2014 were used. These patients participated in one of three studies that were performed by the departments of Nephrology at the University Medical Centers (UMCs) of Groningen, Leiden, Nijmegen and Rotterdam (all in The Netherlands). Details of the study protocols have been published elsewhere; see the Supplementary flow diagram describing the assembly of the cohort[4,8,9]. All patients were included if an MRI-image was available. Subjects were diagnosed with ADPKD based on the modified Ravine criteria[10]. The Medical Ethical Committee of the UMC Groningen approved the protocols of the three studies that were conducted in accordance with the International Conference of Harmonization Good Clinical Practice Guidelines and in adherence to the ethical principles that have their origin in the Declaration of Helsinki. All patients gave written informed consent.

Measurement and collections

All participants collected a 24-hour urine sample the day preceding the MRI-scan, in which urinary albumin concentration was measured. At the outpatient clinic on the day of the MRI, blood pressure was assessed at rest in a supine position with an automatic device (Dinamap; GE Medical Systems) for 15 minutes and weight and height were determined. Blood samples were drawn for determination of creatinine with an enzymatic assay (isotope-dilution mass spectrometry traceable; Modular, Roche Diagnostics), which was used to estimate glomerular filtration rate was using the CKD-EPI equation ($eGFR_{CKD\text{-}EPI}$)[11,12].

Magnetic resonance imaging

All participants underwent a standardised abdominal MRI-protocol without the use of intravenous contrast. For the specific MRI-protocol, see the Supplementary Methods.

Gold standard method; measured total kidney volume (mTKV)

Kidney and liver volumes were measured preferably on the coronal fat saturated T2-single shot fast spin echo sequence. If the T2-weighted images showed too low quality, the MRI was excluded. The kidney and liver volumes were measured using the manually tracing method. The kidney and liver boundaries were manually traced using the commercially available software Analyze Direct 11.0 (Analyze Direct, Inc., Overland Park, KS, USA). The kidney and liver volumes were calculated from the set of contiguous images by summing the products of the area measurements within the kidney or liver boundaries

and slice thickness[6]. Non-renal parenchyma e.g. the renal hilus, was excluded from measurement.

Estimation methods; estimated TKV (eTKV)

The two formulas used to estimate kidney volume were derived from literature[2,7]. We first used the mid-slice method to estimate TKV ($eTKV_{PANK}$)[7]. The mid-slices of the coronal MR images were selected for each kidney separately. The mid-slice was defined as the slice of which the slice number corresponds to the half of the sum of the numbers of the first and the last slice that contained the kidney. If the sum was odd, the mid-slice number was rounded up. $eTKV_{PANK}$ was calculated in mL, with mid-slice area and slice thickness in mm2 and mm, respectively. $eTKV_{PANK}$ was calculated as the sum of the left eKV_{PANK} and right eKV_{PANK}, with left eKV_{PANK} = 0.624 * mid-slice area * number of slices covering the left kidney * slice thickness/1000, and right eKV_{PANK}) = 0.637 * mid-slice area * number of slices covering the right kidney * slice thickness/1000. Second, we used the ellipsoid method to estimate TKV ($eTKV_{ELLIPSOID}$)[2]. Per kidney, length was measured as the average maximal longitudinal diameter measured in the coronal and sagittal plane. Width was obtained from the transversal image at maximum transversal diameter, and depth was measured from the same image perpendicular to the width measurement. $eTKV_{ELLIPSOID}$ was calculated in mL, with length, width and depth in mm, respectively. $eTKV_{ELLIPSOID}$ was calculated as the sum of the left $KV_{ELLIPSOID}$ and right $KV_{ELLIPSOID}$, both derived by the equation $\pi/6$ * (lengthcoronal + lengthsagittal)/2 * width * depth/1000. Of note, to assess $eTKV_{ELLIPSOID}$ no specific software is necessary, in contrast to assessment of mTKV and $eTKV_{PANK}$.

Statistical analyses

All analyses were performed with SPSS, version 22.0 (SPSS Inc). Normality of data was assessed by drawing Q-Q plots. Normal distributed variables are expressed as mean ± standard deviation (SD), whereas non-normal distributed variables are given as median with interquartile range (IQR). Baseline characteristics of the study population are given overall (Table 1) and stratified for eGFR < and ≥ 60 mL/min/1.73m^2 (Supplementary Table 1).

Differences between groups were tested using a two-sample t test for normal distributed and a Mann-Whitney U test for non-normal distributed data. For paired analyses, a paired t test was used for normal distributed and a Wilcoxon-signed rank test for non-normal distributed data. McNemar test was used for paired nominal data. A two-sided $p<0.05$ was considered to indicate statistical significance.

In a test-set of ten patients, stratified for kidney volume and MRI-scanner, kidney volumes were measured and estimated twice by four reviewers. All reviewers were blinded for their previous results. Reproducibility was evaluated by assessing intra- and inter-coefficient of variation (CV) for mTKV, $eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$. The inter-CV was calculated for each of the 10 MRIs as the SD of TKV values assessed by all 4 assessors divided by the mean TKV of that MRI multiplied by 100%. The inter-CV given in the manuscript is the mean of the inter-CVs of these 10 MRIs. The intra-CV was calculated per MRI for each of the 4 assessors as the SD of TKV values divided by the mean TKV multiplied by 100%. Per assessor an average intra-CV was calculated. The intra-CV given in the manuscript is the mean intra-CV (plus SD) of these 4 assessors. We used a paired t test to compare CV's between measured and estimated TKV. This information has also been added.

To investigate whether eTKV correlated with mTKV, orthogonal regression analysis was performed, and Lins' concordance correlation coefficient (CCC) was calculated using all MRI-scans of our cohort[13]. Orthogonal regression uses the least square data modeling technique in which observational errors in both dependent and independent variables are taken into account. Agreement between eTKV and mTKV was evaluated by Bland-Altman analyses, with calculation of agreement limits (95% Confidence Interval [CI]). We used manual tracing as gold-standard for total kidney volume measurement on the x-axis. Performance of the estimation methods compared with mTKV was assessed using bias, precision and accuracy. For cross-sectional analyses, bias is expressed as mean percentage difference (mTKV - eTKV) / mTKV*100%), with positive values indicating an underestimation of mTKV. Precision was defined as 1 standard deviation of bias. Accuracy was calculated as the percentage of eTKV values within 10%, 15% and 20% of mTKV (P_{10}, P_{15}, and P_{20} respectively). To investigate whether bias is dependent on patient or MRI characteristics, we performed regression analyses between bias and various variables i.e. age, length, BMI, liver volume and T1/T2 weighted images in univariate analyses. Differences in bias among the various scanners that were used, were tested with analysis of variance (ANOVA). As standard quality control ~10% of all MRI-scans were measured twice for mTKV, and named this $mTKV_{REPEAT}$. This was done to ensure that the observers maintained low inter-observer variability. These scans were used to assess precision and bias of mTKV.

To investigate whether the estimation methods can accurately detect changes in TKV, data of patients who had follow-up MRIs available were used. For these longitudinal analyses bias is expressed as (%change in mTKV - %change in eTKV). Importantly, all follow-up scans were performed at the same MRI-scanner as at baseline, and TKV was

measured and estimated using the same images series as at baseline, by reviewers blinded for the baseline results.

To assess the consequences of using eTKV instead of mTKV, two analyses were performed. First, the effect on classification based on disease prognosis was assessed. To assess prognosis for clinical care, a classification system is used that categorizes patients into five classes based on thresholds for height corrected TKV (HtTKV) at a given age (A through E, with A indicating the best and E the worst prognosis with respect to future kidney function decline)[2]. In addition, there is a classification indicating whether a patient is suitable for inclusion in clinical trials. This classification contains three classes: patients that should not be included in clinical trials [I], patients whose suitability should be re-evaluated at yearly intervals [II] and patients that are optimal candidates for clinical trials [III])[2]. To assess reclassification, we created 5x5 and 3x3 cross-tabulations using HtTKV limits for their specific age[2]. In these tables the proportion of reclassified participants were calculated when using HteTKV instead of HtmTKV. For this analysis only the "typical cases" were used, as advised for this classification system, defined as MRIs with cysts with bilateral and diffuse distribution, where all cysts contribute similarly to TKV[2]. Second, we assessed what the consequences were for sample size calculation for clinical trials using change in eTKV instead of change in mTKV. Sample size calculations were based on literature[14] and used data of all patients who had longitudinal follow-up data available with respect to change in mTKV and eTKV. The number of patients needed per group was calculated assuming a power of 80% and a two-sided α of 0.05 to detect a percentage difference in TKV growth between treatment groups[15].

RESULTS

Study participants

The study population consisted of 220 patients with ADPKD. We excluded 44 patient, because no T2-weighted images were available to perform both estimation methods. Their characteristics are listed in Table 1. These patients were relatively young with a mean age of 47.0±8.6 years and showed already clear signs of disease. Most patients used antihypertensive medication. Their eGFR was impaired (56.8±20.3 mL/min*1.73m^2), with a wide range in eGFR (from 17.0 to 129.2 mL/min*1.73m^2). Urinary albumin excretion (46.7 [21.2-88.2] mg/24h) and total kidney volume (1.96 [1.28-2.82] L) were increased.

Table 1. *Participants' characteristics.*

	Whole study group	Patients with follow-up	Test-set
N	220	48	10
Age (y)	47.0 ± 8.6	39.2 ± 7.4	44.3 ± 10.2
Male (% (n))	51.8 (114)	70.8 (34)	30 (3)
Body mass index (kg/m^2)	26.9 ± 4.3	26.3 ± 3.4	27.1 ± 7.2
Body surface area (m^2)	2.0 ± 0.2	2.1 ± 0.2	1.96 ± 0.2
Diastolic blood pressure (mm Hg)	82.2 ± 9.5	82.6 ± 8.8	85.4 ± 11.0
Systolic blood pressure (mm Hg)	132.7 ± 13.0	132.9 ± 11.6	134.1 ± 18.0
Antihypertensive medication (% (n))	86.4 (190)	81.3 (39)	90 (9)
Plasma creatinine (mmol/L)	125.5 ± 39.7	102.1 ± 31.7	127.4 ± 20.4
eGFR (mL/min/1.73m^2)	56.8 ± 20.3	79.7 ± 22.6	49.6 ± 10.2
24h Urine volume (L)	2.36 ± 0.77	2.48 ± 0.87	2.60 ± 0.80
Albuminuria (mg/24h)	46.7 (21.2 – 88.2)	46.2 (19.0 – 181.0)	67.9 (17.0 – 95.4)
Total kidney volume (L)	1.96 (1.28 – 2.82)	1.79 (1.36 – 2.56)	1.78 (1.37 – 2.86)
- Left kidney volume (L)	1.00 (0.67 – 1.52)	0.99 (0.73 – 1.39)	0.92 (0.70 – 1.62)
- Right kidney volume (L)	0.92 (0.60 – 1.38)	0.80 (0.57 – 1.17)	0.91 (0.67 – 1.24)
Liver volume (L)	2.74 (1.73 – 3.07)	NA	1.76 (1.62 – 3.64)

Reproducibility of mTKV and eTKV

Table 2 shows a test-set for assessing reproducibility The average intra-observer CV was 1.8% for mTKV and 2.6% for total liver volume, whereas the inter-observer CV was 2.3% and 3.5%, respectively. The variability for $eTKV_{ELLIPSOID}$ was significantly higher than for mTKV, whereas for $eTKV_{PANK}$ no significant differences were found when compared to mTKV. Analysis time was approximately 55 minutes per MRI for mTKV and 65 minutes for total liver volume, with higher analysis times in case of larger organs. The average time needed per MRI to estimate TKV using the mid-slice method was 15 minutes and using the ellipsoid method 5 minutes.

Performance of the TKV estimation methods

In the cohort for cross-sectional analyses, the correlations of mTKV vs. $mTKV_{REPEAT}$, $eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$ are shown in Figure 1.

Supplementary Figures 1 and 2 shows these correlations for left and right kidneys separately. High correlations were observed for all three methods: $mTKV_{REPEAT}$ r=0.998 (p<0.001), $eTKV_{ELLIPSOID}$ r=0.989 (p<0.001), and $eTKV_{PANK}$ r=0.990 (p<0.001). Figure 1 also shows Bland-Altman plots of mTKV vs. the percentage difference between mTKV and

Figure 1. *Cohort for cross-sectional analyses: Associations between measured total kidney volume (mTKV) and repeated mTKV ($mTKV_{REPEAT}$) (upper panels), estimated TKV using the ellipsoid method ($eTKV_{ELLIPSOID}$) (middle pannels) and the mid-slice method ($eTKV_{PANK}$) (lower panels). Left panel shows scatter plots (solid line representing the line of identity and the dotted line the actual regression line), whereas the right panel shows Bland-Altman plots (solid line indicating no difference and dotted lines representing mean difference [i.e. bias] with 95% confidence interval).*

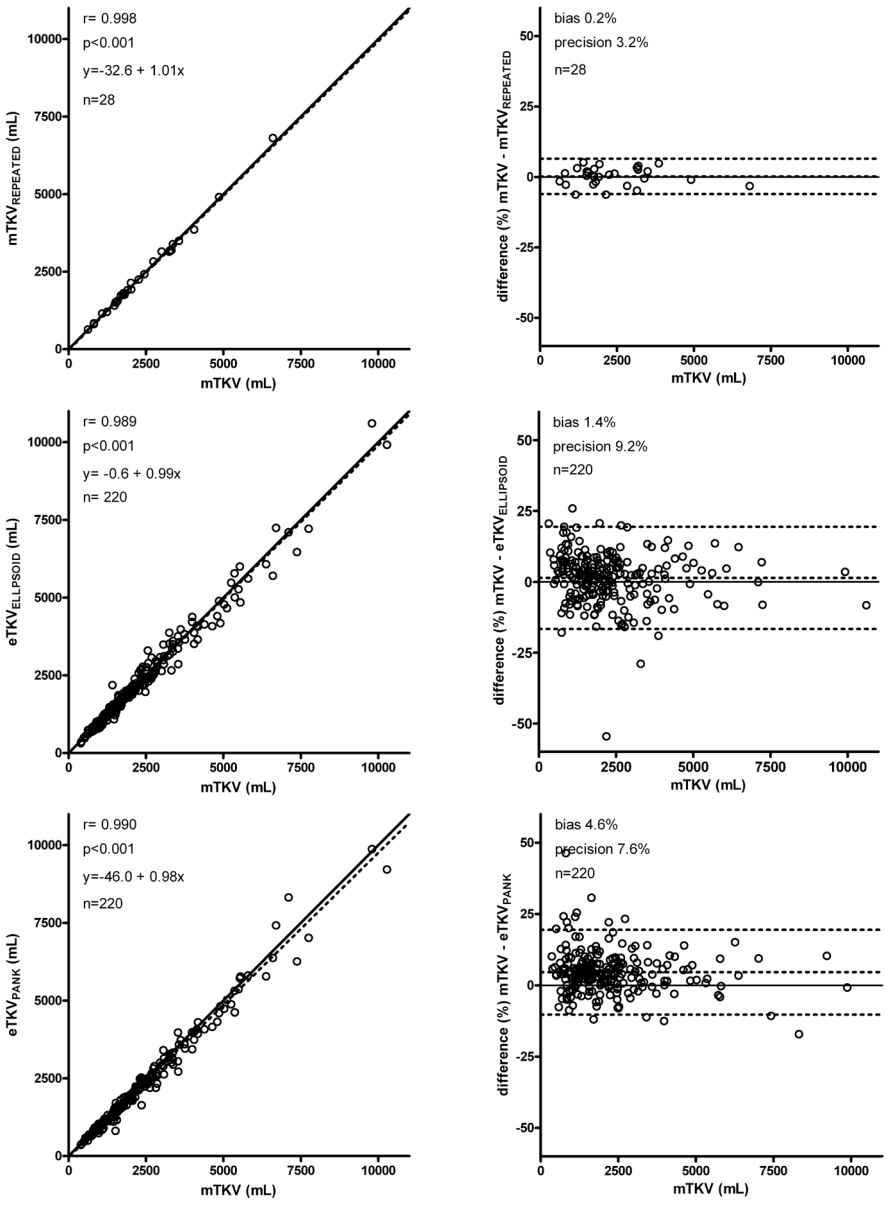


Table 2. *Test-set for assessing reproducibility. Intra- and inter-observer coefficient of variation (CV) for measured total kidney volume (mTKV) and for estimated total kidney volume using the ellipsoid method ($eTKV_{ELLIPSOID}$) and the mid-slice method ($eTKV_{PANK}$). All CV were calculated based on 10 patients.*

	Left kidney	Right kidney	Both kidneys
mTKV			
- Intra-observer CV (%)	2.3	1.9	1.8
- Inter-observer CV (%)	2.6	2.9	2.3
$eTKV_{ELLIPSOID}$			
- Intra-observer CV (%)	4.9*	4.3*	3.9*
- Inter-observer CV (%)	6.0*	8.5*	6.3*
$eTKV_{PANK}$			
- Intra-observer CV (%)	3.8	3.1	3.0
- Inter-observer CV (%)	4.2	3.1	3.4

**p-value <0.05 for difference in intra- or inter-observer CV eTKV vs. corresponding value of mTKV.*

$mTKV_{REPEAT}$ and both eTKV methods. $mTKV_{REPEAT}$ showed low bias (mean 0.02%±3.2%). eTKV also did not systematically over- or underestimate mTKV (bias of 1.4%±9.2% and 4.6%±7.6% for $eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$, respectively, Table 3). Bias for $eTKV_{PANK}$ was significantly higher than for $mTKV_{REPEAT}$ (p=0.005), whereas bias for $eTKV_{ELLIPSOID}$ did not significantly differ from $mTKV_{REPEAT}$ (p=0.4). Given the lower SD, $mTKV_{REPEAT}$ had a better precision and therefore better performance when compared to $eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$.

In addition, when these analyses were repeated with ADPKD patients stratified for eGFR, we observed no significant difference in bias for $eTKV^{ELLIPSOID}$ and $mTKV^{REPEAT}$ in patients with eGFR ≥ 60 mL/min*1.73m^2 and eGFR <60 mL/min*1.73m^2 (p=0.2 and p=0.3, respectively). Between $eTKV^{PANK}$ and $mTKV^{REPEAT}$, we observed also no significant difference in patients with eGFR < 60 mL/min*1.73m^2 (p=0.2) and in patients with eGFR ≥60 mL/min*1.73m^2 (p=0.9) Supplementary Table 2 shows bias, accuracy for eTKV stratified by eGFR.

When investigating factors associated with bias, it appeared that liver volume was associated with bias in $eTKV^{PANK}$ (p=0.044), but not with $eTKV^{ELLIPSOID}$ (p=0.1). Bias was not associated with age (p=0.5 and p=0.6), height (p=0.8 and p=0.14) and strength of magnetic field (p=0.8 and p=0.7), respectively for $eTKV^{ELLIPSOID}$ and $eTKV^{PANK}$.

Ability to detect changes in TKV when using estimation methods

Follow-up data for TKV were available for 48 patients. The baseline characteristics for the longitudinal cohort are given in Table 1.

These patients were younger, showed less signs of disease, with a higher eGFR (79.7±22.6 ml/min*1.73m^2), but similar urinary albumin excretion (46.2 [19.0-181.0] mg/24h). During a follow-up of 3.0 years their mTKV increased from 1.79 (1.36-2.56) to 2.18 (1.55-2.73) L (p<0.001). The median difference during follow-up was 0.25 (0.04-0.54), 0.30 (0.08-0.86) and 0.28 (0.08-0.54) L for mTKV, $eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$, respectively (Table 4). Change in eTKV compared to change in mTKV was not significantly different for both estimation methods (p=0.2 and p=0.5 for $eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$, respectively). Figure 2 plots the percentage change in mTKV vs. the percentage change in eTKV. High concordance correlations were observed for $eTKV_{ELLIPSOID}$ (r=0.798, p<0.001) and $eTKV_{PANK}$ (r=0.866, p<0.001). Percentage change in eTKV did not show systematic under- or overestimation, with bias and precision (% change mTKV - % change eTKV) -2.2%±10.3% and -1.8%±8.3% for $eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$, respectively (Figure 2). In the majority of the patients, bias for change in eTKV was between -10% and 10% (72.3% and 74.5% of patients for $eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$, respectively).

Table 3. *Cohort for cross-sectional analyses: Performance of the ellipsoid method and the mid-slice method to estimate total kidney volume.*

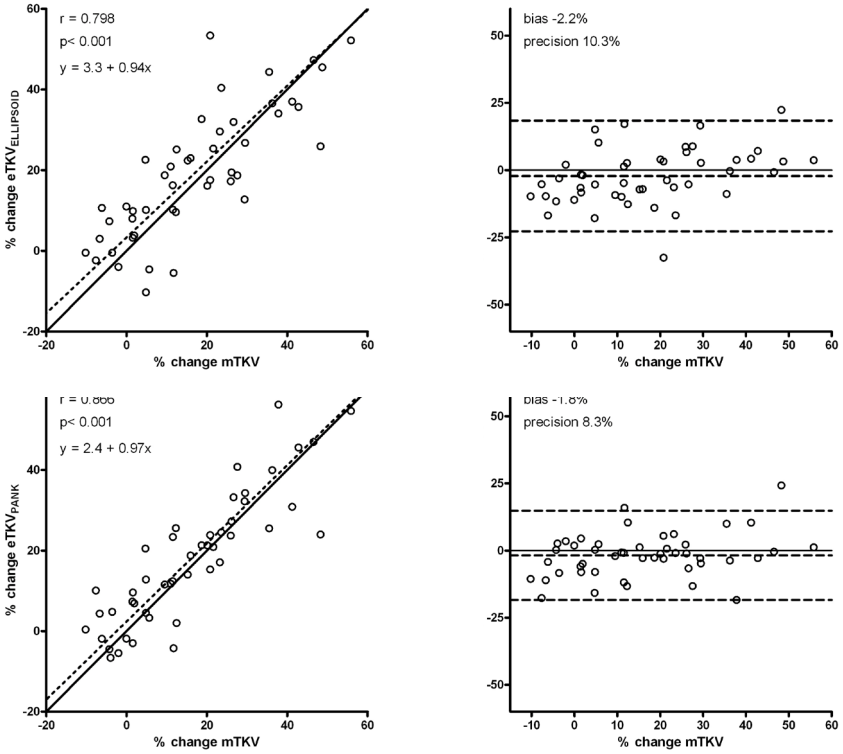
	$eTKV_{ELLIPSOID}$	**$eTKV_{PANK}$**	**$mTKV_{REPEAT}$**	**p-value***
Number of patients	220	220	28	
Left kidney volume (L)	1.03 (0.65 – 1.48)	0.95 (0.63 – 1.45)	1.03 (0.75 – 1.78)	0.3
- Bias (%)	-0.7	5.6	0.1	0.9
- Precision (%)	11.8	9.7	3.6	
Right kidney volume (L)	0.90 (0.57 – 1.37)	0.88 (0.54 – 1.33)	0.98 (0.67 – 1.51)	0.003
- Bias (%)	2.0	3.2	0.4	0.048
- Precision (%)	12.4	11.1	3.9	
Total kidney volume (L)	1.93 (1.25 – 2.82)	1.81 (1.17 – 2.62)	1.92 (1.51 – 3.18)	0.004
- Bias (%)	1.4	4.6	0.2	0.4
- Precision (%)	9.2	7.6	3.2	
- Accuracy				
P_{10}	78.1	82.1	100	<0.001
P_{15}	92.7	93.6	100	<0.001
P_{20}	97.7	96.4	100	<0.001
- CCC	0.988	0.987	0.998	

Note: Unless otherwise indicated, values for categorical variables are given as percentages; values for non-parametric are given as median and interquartile range. P values are calculated by paired t test when normally distributed, Wilcoxon signed-rank test when non-normally distributed for continues variables and McNemar test for nominal variables. Abbreviations and definitions: Bias, mean % difference between mTKV and eTKV; Precision, 1 standard deviation of bias; Accuracy, percentage of eTKV values within 10% (P10), 15% (P15) and 20% (P20) of their corresponding mTKV value; CCC, concordance correlation coefficient.

** $mTKV^{REPEAT}$ vs. $eTKV^{ELLIPSOID}$ | % $mTKV^{REPEAT}$ vs. $eTKV^{PANK}$*

The consequences of using percentage change in eTKV instead of percentage change in mTKV as endpoint for sample size calculation for randomized controlled trials were assessed using data of the 48 ADPKD patients of which follow-up data were available. We calculated the number of study participants per treatment group needed to be enrolled to demonstrate a certain percentage decrease in rate of growth in TKV. The results are shown in Supplementary Table 3.

Figure 2. *Cohort for longitudinal analyses: Associations between percentage change in measured total kidney volume (mTKV) and percentage change in estimated total kidney volume (eTKV) using the ellipsoid method and the mid-slice method in 48 ADPKD patients who had follow-up data available. Left panel shows scatter plots (solid line representing the line of identity and dotted line the actual regression line), whereas the right panel shows Bland-Altman plots (solid horizontal line indicating no difference, and dotted lines representing mean difference [i.e. bias] with 95% confidence interval).*



To detect for instance a 30% decrease in rate of growth in mTKV over a period of 3 years, 186 patients are needed per treatment group, whereas for $eTKV^{ELLIPSOID}$ and $eTKV^{PANK}$ these numbers are 122 and 143, respectively.

Table 4. *Cohort for longitudinal analyses: Baseline and follow-up total kidney volume (TKV) data in 48 ADPKD patients with follow-up data available.*

	Baseline (L)	Follow-up (L)	Change (L)	Change (%)
		Left kidney		
mTKV	0.99 (0.74 – 1.39)	1.23 (0.83 – 1.56)	0.13 (0.01 – 0.29)	15.0 ± 18.7
$eTKV_{ELLIPSOID}$	1.03 (0.70 – 1.44)	1.26 (0.85 – 1.58)	0.10 (0.04 – 0.37)	17.7 ± 18.1
$eTKV_{PANK}$	0.92 (0.68 – 1.24)	1.10 (0.78 – 1.44)	0.17 (0.04 – 0.36)*	19.7 ± 19.0*
		Right kidney		
mTKV	0.80 (0.57 – 1.17)	0.99 (0.68 – 1.29)	0.13 (0.06 – 0.25)	19.4 ± 18.6
$eTKV_{ELLIPSOID}$	0.81 (0.58 – 1.10)	1.04 (0.65 – 1.39)	0.14 (0.04 – 0.29)	23.1 ± 22.8
$eTKV_{PANK}$	0.78 (0.60 – 1.14)	0.90 (0.65 – 1.24)	0.13 (0.04 – 0.24)	17.0 ± 19.6
		Both kidneys		
mTKV	1.79 (1.36 – 2.56)	2.18 (1.55 – 2.73)	0.25 (0.04 – 0.54)	16.7 ± 17.1
$eTKV_{ELLIPSOID}$	1.86 (1.32 – 2.75)	2.39 (1.50 – 2.80)	0.30 (0.08 – 0.86)	19.3 ± 16.1
$eTKV_{PANK}$	1.79 (1.12 – 2.43)	2.03 (1.49 – 2.63)	0.28 (0.08 – 0.54)	17.8 ± 16.1

*Note: Unless otherwise indicated, values for continuous variables are given as mean standard deviation (if parametric) or median [interquartile range] if nonparametric. Abbreviations: mTKV, measured total kidney volume; $eTKV^{ELLIPSOID}$, total kidney volume estimated using ellipsoid method; eTKVPANK, total kidney volume estimated using mid-slice method. Nosignificant differences between change in eTKV vs. change in mTKV were noted, but only at change in left $eTKV^{PANK}$ as indicated with an asterisks. * p-value <0.05.*

Consequences of using eTKV instead of mTKV

When using the eTKV methods instead of mTKV for risk classification with respect to prognosis for rapid kidney function decline, we excluded the radiologically atypical ADPKD cases (n=27), as advised for this classification system. 93.3% ($eTKV^{ELLIPSOID}$) and 90.2% ($eTKV^{PANK}$) of the patients were reclassified to their original risk categories (Table 5), whereas for both estimation methods, less than 1.6% of the patients were reclassified to a higher risk category and less than 8.5% to a lower risk category. For classification for selection of patients for clinical trials, we observed that 97.4% ($eTKV^{ELLIPSOID}$) and 95.9% ($eTKV^{PANK}$) of the patients were reclassified to their original categories. No patients were reclassified to a higher risk category when using $eTKV^{ELLIPSOID}$ and only 1 patient when using $eTKV^{PANK}$ (Table 5).

Table 5. *Reclassification for staging into risk categories for rapid kidney function decline for clinical care (A-E) and for selection of patients for clinical trials based on thresholds for height corrected TKV at a given age (I-III) using ellipsoid method ($eTKV_{ELLIPSOID}$) and using mid-slice method ($eTKV_{PANK}$) instead of mTKV.*

		$eTKV_{ELLIPSOID}$						$eTKV_{PANK}$					
		A	**B**	**C**	**D**	**E**		**A**	**B**	**C**	**D**	**E**
mTKV	**A**	5					**A**	4	1			
	B		28				**B**	1	27			
	C		5	66	2		**C**		6	65	2	
	D			4	47	1	**D**			6	45	
	E				1	35	**E**				3	33
		$eTKV_{ELLIPSOID}$						$eTKV_{PANK}$				
		I	**II**	**IIII**				**I**	**II**	**IIII**		
mTKV	**I**	5					**I**	4	1			
	II		28				**II**	1	27			
	IIII		5	155			**IIII**		6	150		

DISCUSSION

This study was conducted to investigate whether TKV can be estimated accurately using the mid-slice and ellipsoid methods in a group of ADPKD patients with a wide range of kidney function. In a test-set of ten ADPKD patients we found that both estimation methods were highly reproducible. In our study cohort of 220 ADPKD patients both methods showed low bias, high precision and high accuracy when compared to measured TKV (mTKV). This held for the overall cohort, as well as for patients with higher and lower eGFR. In the 48 patients who had follow-up MRIs available, change in estimated TKV (eTKV) was not different from change in mTKV for both methods.

Assessment of TKV using the gold standard method is time consuming and needs specific software, which limits its applicability for clinical care. Methods have therefore been sought to estimate TKV in a more feasible way. Two methods have been published recently,[2,7] which, however, have yet not been validated. This formed the rationale to perform the present study. For determination whether these estimation methods can be used to assess TKV, it is of importance to answer the following five questions.

First of all, it is important to investigate what the reliability of the gold-standard method is. In our study we found that the variability in volumetric assessment by manual tracing (i.e. the gold standard method) was very low. In general, T1-weighted images instead of

T2-weighted images are used for volumetry in ADPKD, because researchers want to align with the original CRISP methodology. However, when the CRISP study started, gadolinium enhanced T1-weighted MR images were used. Because of the potential side effects of gadolinium, the use of this contrast agent has since been discouraged. Bae et al showed in 2009 that unenhanced T1-weighted volumes were significantly lower than contrast-enhanced T1-weighted volumes[16]. These differences were more pronounced in smaller kidneys, because in such cases the ratio of kidney boundaries area to kidney volume is higher. Bae et al mentioned that one should therefore consider using T2 MR imaging for the quantification of TKV, because the high kidney tissue-contrast and hyperintense renal cysts in T2 images help delineate the kidney boundaries against the background tissues when compared to T1-weighted images. At that time T2-weighted imaging required longer scanning time and was subjected to increased variation in image quality because of motion artefacts, and was therefore not feasible. Nowadays T2 weighted scanning time is shorter and respiratory-triggered to avoid motion artefacts has become available. In our experience this sequence has the best quality in visualising the polycystic kidneys. We therefore choose T2-weighted images instead of T1-weighted for our study.

Second, do these estimation methods show low variability? The variability in mTKV versus $eTKV_{PANK}$ was not significantly different and satisfactory low. The variability in $eTKV_{ELLIPSOID}$ was significantly higher compared to mTKV, meaning that this method is slightly more operator-dependent than the mid-slice method, but still low. In line, reclassification to another risk category for rapid kidney function decline for clinical care (Irazabal classes A-E) happened infrequent when using $eTKV_{PANK}$, as well as $eTKV_{ELLIPSOID}$ (Table 5). Given these results, and because $eTKV_{ELLIPSOID}$ is more convenient (shorter duration per MRI and assessment possible using standard MRI software) we advise to use in clinical care $eTKV_{ELLIPSOID}$ rather than $eTKV_{PANK}$ for risk assessment.

Third, does the estimation method show good agreement with the gold standard method? We found for both estimation methods that eTKV correlated strongly with mTKV. Although bias and precision showed again better values for $mTKV_{REPEAT}$ (0.02% and 3.2%, respectively), the results for $eTKV_{ELLIPSOID}$ as well as $eTKV_{PANK}$ for were good. Bias was low for $eTKV_{ELLIPSOID}$ and $eTKVP_{PANK}$, (1.4% and 4.6 %, respectively), although for $eTKV_{PANK}$ slightly (but significantly) higher than for $mTKV_{REPEAT}$. In addition, precision was reasonable, now with slightly better results for $eTKV_{ELLIPSOID}$ ($eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$ 9.2% and 7.6%, respectively, Table 3). Consequently we found good accuracy for both estimation methods ($eTKV_{PANK}$ P20 96.4%, and $eTKV_{ELLIPSOID}$ P20 97.7%). Our findings with respect to accuracy are consistent with the values obtained in the cohort in which the ellipsoid method

was developed (P10 70.3% vs. 78.1% in the present study)[2]. When stratified for kidney function our results with respect to bias suggest that the mid-slice method may be less accurate in ADPKD patients with lower kidney function, who generally have larger kidneys. Besides these statistical data, consequences for clinical care should be investigated when answering the question whether estimation methods show good agreement with the gold standard method. Irazabal et al proposed a classification system for ADPKD patients to assess their risk for rapid kidney function decline and to guide selection of patients for clinical trials[2]. This classification system uses thresholds defined on age and height corrected TKV. We investigated the percentage of patients that are reclassified when using eTKV instead of mTKV. In the classification system for risk assessment, we observed that only a limited percentage of patients was reclassified, and that these patients were especially reclassified to a lower risk category (Table 5). No fundamental differences in results were observed for the two TKV estimation methods, and only one patient was reclassified to a risk category that would preclude treatment when using $eTKV_{PANK}$ (category B).

Fourth, can the estimation method detect changes in TKV over time? As far as we are aware no study has yet investigated the performance of estimation methods to assess changes in TKV. In our analyses, we found a high concordance correlation between change in mTKV and change in $eTKV_{PANK}$ and $eTKV_{ELLIPSOID}$ during three years follow-up, and no difference between change in mTKV and change in $eTKV_{PANK}$ and $eTKV_{ELLIPSOID}$ (Table 5). Consequently, when data are used of change in eTKV instead of change in mTKV, similar numbers of patients have to be included in clinical trials to be able to show a decrease in rate of growth in TKV (Table 5). These longitudinal results may seem surprising, because they appear to be in contrast with our cross-sectional data, where we showed that mTKV shows better reliability than $eTKV_{PANK}$ and $eTKV_{ELLIPSOID}$, albeit that these differences were small. In our opinion, this may be due to two explanations. It could well be that with the eTKV methods a systematic error is made in an individual patient in assessing TKV at baseline, for instance due to a peculiar shape of a cystic kidney, but that the same error is made during follow-up, because the shape of the cystic kidney has not changed. In this way a systematic error in baseline eTKV will not translate in bias in change in eTKV during follow-up on a patient level. In addition, the natural variability in growth in TKV between patients may be that high, that the limited variability that is added by using eTKV is not relevant when assessing mean change in TKV on a group level.

The fifth and last question to be answered is whether the estimation method is feasible from a clinical point of view. To estimate TKV using the mid-slice method, special software is necessary to measure the mid-slice area, limiting clinical applicability. In contrast, all clinicians can estimate TKV by the ellipsoid method using standard MRIs without special software. Furthermore, the ellipsoid method requires less time to estimate TKV than

using the mid-slice method, and both methods require far less time than assessment of mTKV with the gold standard method, i.e. manually tracing method.

The answers to the above questions indicate that, although eTKV may be slightly less precise than mTKV using manual tracing method, it can be used with confidence in clinical care. Because the two eTKV methods show numerically hardly any differences with respect to bias, precision and accuracy, and no difference in ability to detect changes in eTKV, the more feasible ellipsoid method is to be preferred over the mid-slice method. Whether this conclusion is also valid for the use of $eTKV_{ELLIPSOID}$ instead of mTKV for clinical trials needs confirmation. To investigate this issue, the results of these two assessment techniques should be compared in large-scale trials between different intervention groups using MRIs obtained at baseline as well as during follow-up. Our data form the rationale to perform such studies.

A limitation of the present study is that our results hold primarily true for the cross-sectional correlation between mTKV and eTKV. Our results for follow-up data should be interpreted with caution, because the results are based on a limited number of patients. Strengths of this study are that we investigated both estimation methods in a group of ADPKD patients with relatively well-preserved as well as impaired kidney function, and that we are the first to externally validate both estimation methods.

In conclusion, we demonstrated that both methods to estimate TKV perform relatively well in ADPKD patients overall, as well as in patients with preserved as well as impaired kidney function. In addition, both estimation methods detect relatively accurate changes in TKV over time. Because of these results and the higher feasibility, we advise to use the ellipsoid method for TKV estimation in clinical care. Whether this method can also be used for clinical trials deserves further study.

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Chapter 9

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SUPPLEMENTARY MATERIAL

Supplementary methods

Magnetic resonance imaging

The UMC Groningen used a 1.5-Tesla MR scanner (Magneto Avanto, Siemens, Erlangen, Germany) and a 3-Tesla research MR scanner (Intera, Philips, Eindhoven, the Netherlands). All other centers used a 1.5-Tesla MRI-scan [UMC Leiden: Philips Healthcare, Eindhoven, the Netherlands; UMC Rotterdam: GE Medical Systems, Buckinghamshire, United Kingdom; and the UMC Nijmegen: Avanto Siemens, Erlangen, Germany]. Coils were placed onto the anterior and posterior abdominal walls directly over the kidneys. A short scout was scanned to localize the kidneys. Subsequently four series of images were scanned. Two T2-fast multislice spoiled gradient echo were scanned coronal and transversal, with slice thickness of 4 mm, gap/spacing 0 mm, FOV 35 cm, matrix 256*256, TE ≈ 2 ms, TR ≈ 7 ms, Flip Angle 40-50°. Thereafter a T2-single shot fast spin echo was scanned coronal (same characteristics, but different TR's and TE's per brand MRI-scanner: TE ≈ 100 ms for Siemens, TE ≈ 190 ms and TR ≈ max. 1400 ms for GE and ≈ 70 ms and TR ≈ max. 1900 ms for Philips) and a T1-3D spoiled gradient echo coronal (same characteristics except TR ≈ 4 ms and Flip Angle ≤15°). At the beginning and the end of the scan sequence had to be at least 1 slice not containing liver and kidney tissue. When a 35 cm FOV was insufficient, the FOV could be increased. Preferably, both kidneys as well as the liver, including all cysts, had to be covered within one sequence of images. When such a sequence could not be scanned, two separate sequences for liver and kidneys were allowed. The obtained MR images were anonymized and sent via a secured server to the central reading facility at the UMC Groningen, where kidney and liver volume were measured. Nine medical students were specifically trained to measure TKV. During their training period, they measured 40 kidney volumes and 20 liver volumes under supervision and guidance of an experienced MRI-technician using a standard operating procedure. After these students completed their training, they were allowed to measure TKV.

Supplementary Table 1. *Baseline characteristics stratified by eGFR*

	eGFR ml/min/1.73m²		
	< 60	**≥ 60**	**p-value**
N	145	75	
Age (y)	49.5 ± 7.6	42.3 ± 8.5	<0.001
Male (% (n))	49.0 (71)	57.3 (43)	0.2
Body mass index (kg/m²)	27.0 ± 44.0	26.7 ± 4.8	0.1
Body surface area (m²)	2.04 ± 0.22	2.04 ± 0.22	0.7
Diastolic blood pressure (mm Hg)	82.7 ± 10.0	81.4 ± 8.5	0.2
Systolic blood pressure (mm Hg)	133.8 ± 12.9	130.7 ± 12.9	0.9
Antihypertensive medication (% (n))	87.6 (127)	78.3 (59)	0.08
Plasma creatinine (mmol/L)	141.8 ± 38.4	93.9 ± 16.2	<0.001
eGFR (mL/min/1.73m²)	45.5 ± 9.0	78.8 ± 17.7	<0.001
24h Urine volume (L)	2.41 ± 0.75	2.28 ± 0.81	0.8
Albuminuria (mg/24h)	53.4 (26.5 - 103.9)	37.8 (16.7 - 87.7)	0.07
Total kidney volume (L)	2.14 (1.42 - 3.14)	1.68 (1.16 - 2.39)	0.02
- Left kidney volume (L)	1.10 (0.72 - 1.73)	0.92 (0.62 - 1.32)	0.1
- Right kidney volume (L)	1.02 (0.66 - 1.51)	0.75 (0.54 - 1.05)	0.004
Liver volume (L)	2.78 (1.71 - 3.20)	2.56 (1.83 - 3.03)	0.5

Unless otherwise indicated, values for categorical variables are given as percentages; values for continuous variables are given as mean ± standard deviation if parametric or median (interquartile range) if non parametric. Abbreviations are: eGFR, estimated glomerular filtration rate (CKD-EPI equation). P-values indicate differences between eGFR < 60 and ≥ 60. P-values are calculated by t test when normally distributed and by Mann-Whitney U test when non-normally distributed.

Supplementary Table 2. *Performance of the ellipsoid method and the mid-slice method to estimate total kidney volume ($eTKV_{ELLIPSOID}$ and $eTKV_{PANK}$, respectively), stratified for eGFR ≥60 en <60 ml/min/1.73m²*.

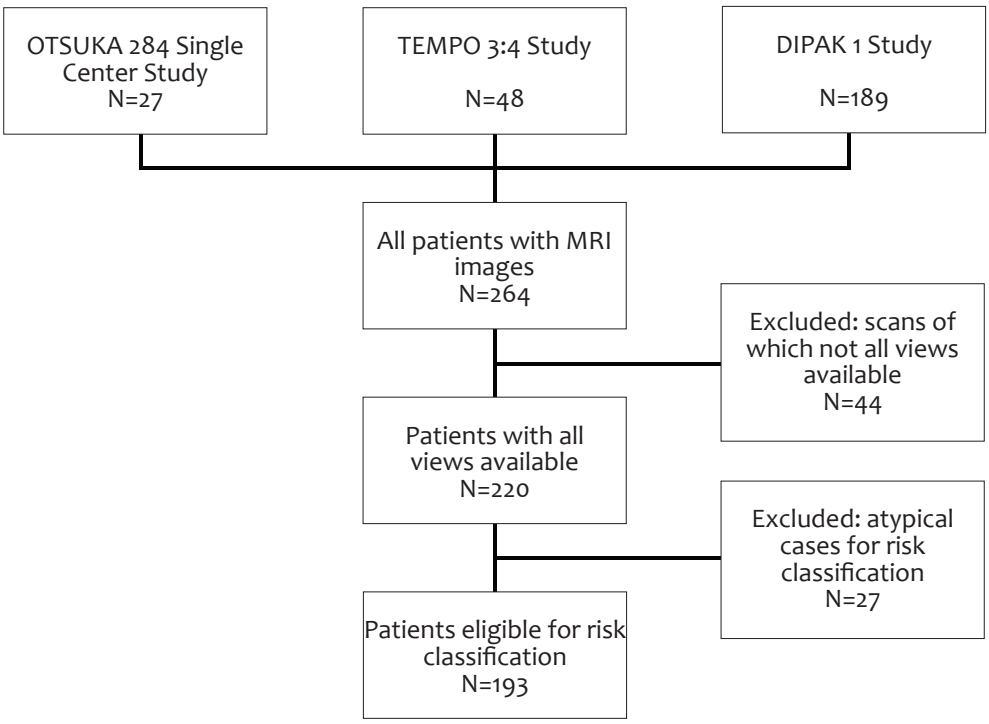
	$eTKV_{ELLIPSOID}$			$eTKV_{PANK}$		
eGFR	**≥60**	**<60**	**p-value**	**≥60**	**<60**	**p-value**
N	75	145		75	145	
Left kidney volume (L)	0.99 (0.60 - 1.27)	1.12 (0.69 - 1.77)	0.1	0.84 (0.61- 1.20)	1.02 (0.65 - 1.56)*	0.1
- Bias (%)	-1.2	-0.5	0.6	4.4	6.2	0.5
- Precision (%)	12.2	11.7		10.7	9.1	
Right kidney volume (L)	0.72 (0.52 - 1.10)	0.99 (0.63 - 1.49)	0.008	0.75 (0.50 - 1.11)	0.99 (0.60 - 1.46)	0.04
- Bias (%)	0.4	2.8	0.9	0.2	4.7	0.5
- Precision (%)	12.2	12.5		9.1	11.8	
Total kidney volume (L)	1.75 (1.18 - 2.39)	2.12 (1.14 - 3.12)	0.03	1.64 (1.11 - 2.34)	2.07 (1.31 - 3.00)	0.06
- Bias (%)	0.7	1.7	0.9	2.7	5.5	0.3
- Precision (%)	8.8	9.3		6.6	7.9	
- Accuracy						
P_{10}	77.3	78.9	0.8	90.5	77.8	0.02
P_{15}	90.7	93.8	0.4	94.7	93.1	0.6
P_{20}	97.3	100	0.8	97.4	95.9	0.6
- CCC	0.986	0.988		0.989	0.985	

P-values are calculated with independent t tests when normally distributed and with Wilcoxon signed-rank tests when non-normally distributed for unpaired data, and with paired t tests and McNemar tests for paired data. Abbreviations and definitions: $eTKV_{ELLIPSOID}$, estimated total kidney volume using ellipsoid method; $eTKV_{PANK}$, estimated total kidney volume using mid-slice method; eGFR, estimated glomerular filtration rate. Accuracy, percentage of estimated total kidney volume values within 10% (P10), 15% (P15) and 20% (P20) of their corresponding measured total kidney volume value (TKV). Bias, mean % difference between mTKV and eTKV. Precision, 1 standard deviation of bias; CCC, concordance correlation coefficient. P values for $eTKV_{ELLIPSOID}$ ≥60 vs. <60 are calculated by t test when normally distributed and Mann-Whitney U test when non-normally distributed.

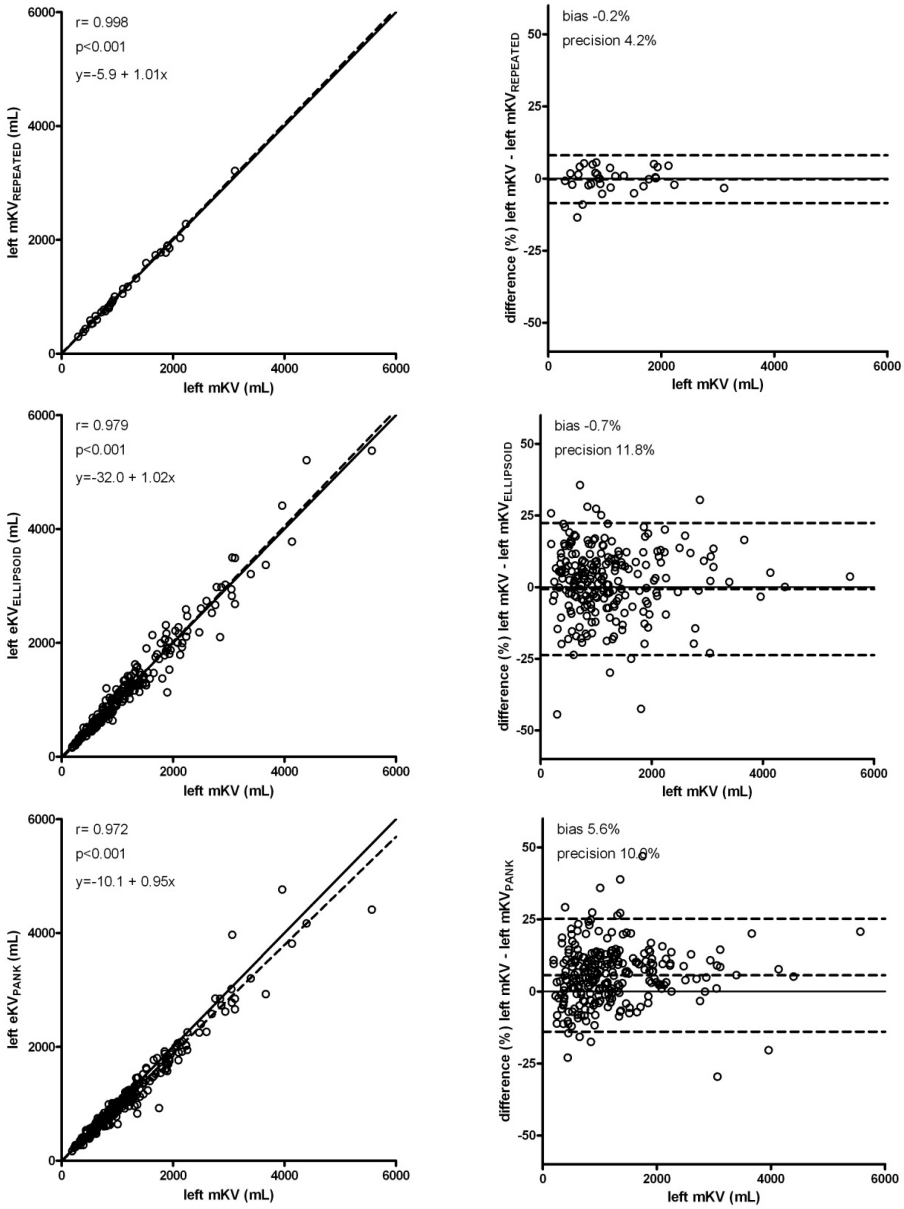
Supplementary Table 3. *Number of participants per treatment group needed for randomized controlled trials to be able to show a specific % difference in growth in total kidney volume over a period of three years when using gold standard total kidney volume (mTKV) or estimated kidney volume using the ellipsoid method ($eTKV_{ELLIPSOID}$) or mid-slice method ($eTKV_{PANK}$).*

	mTKV	$eTKV_{ELLIPSOID}$	$eTKV_{PANK}$
20%	417	274	332
30%	186	122	143
40%	105	69	81
50%	67	44	52

Supplementary Figure 1. *Flow diagram of the study design and classification. We reviewed all available abdominal MRI-scan of patients with ADPKD who participated in the Otsuka 284 single Center Study, TEMPO 3:4 study and DIPAK 1 Study from 2007 through 2014. 264 patients were included of whom 44 were excluded, because not all views (coronal sagittal, transversal) were available. 193 patients were eligible for risk classification and 27 patients were excluded due to atypical cases of ADPKD. The classification was based on Irazabel et al.*



Supplementary Figure 2. *Associations between measured left kidney volume (mKV) and repeated mKV (mKV_{REPEAT}) (upper panels), estimated left kidney volume using ellipsoid method ($eKV_{ELLIPSOID}$) (middle panels) and using mid-slice method (eKV_{PANK}) (lower panels). Left panel shows scatter plots (solid line representing the line of identity and the dotted line the actual regression line), whereas the right panel shows Bland-Altman plots (solid line indicating no difference, and dotted lines representing mean difference [i.e. bias] and 95% confidence interval).*



Supplementary Figure 3. *Associations between measured right kidney volume (mKV) and right repeated mKV (mKV_{REPEAT}) (upper panels), estimated right kidney volume using ellipsoid method ($eKV_{ELLIPSOID}$) (middle panels) and using mid-slice method (eKV_{PANK}) (lower panels). Left panel shows scatter plots (solid line representing the line of identity and the dotted line the actual regression line), whereas the right panel shows Bland-Altman plots (solid line indicating no difference, and dotted lines representing mean difference [i.e. bias] and 95% confidence interval).*